

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Timo Heinrich et al.

Examiner: Noble E. Jarrell

Serial No.: 10/560,737

Group Art Unit: 1624

Filed: December 15, 2005

For: INDOLE DERIVATIVES AS SEROTONIN REUPTAKE INHIBITORS

**APPEAL BRIEF**

Mail Stop: AF  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on January 6, 2009, please consider the following.

The Appeal Brief fee of \$ 540.00 is filed/paid herewith. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

**(i) REAL PARTY IN INTEREST**

This application is assigned to Merck Patent GmbH, by means of an Assignment recorded at Reel 017381, Frame 0782.

**(ii) RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

**(iii) STATUS OF CLAIMS**

Claims 1-4, 6-9, 12, 14 and 15 are pending.

Claims 5, 10, 11 and 13 are canceled.

Claims 1-4, 6-9 and 12-14 are rejected.

Claims 1-4, 6-9 and 12-14 are on appeal.

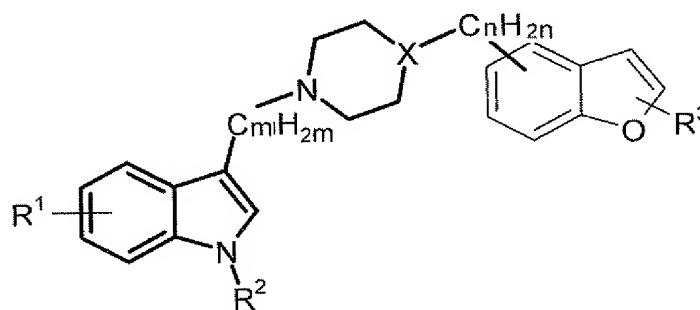
Claim 15 is apparently allowable.

**(iv) STATUS OF AMENDMENTS**

Applicants Amendment Under 37 C.F.R. 1.116 filed December 8, 2008, has been entered. See item 7 of the Advisory Action mailed January 5, 2009.

**(v) SUMMARY OF CLAIMED SUBJECT MATTER**

The invention is directed to compounds of the formula I



X = N or CH,

R<sup>1</sup>, R<sup>3</sup> = independently of one another H, OH, OA, CN, Hal, COR<sup>4</sup> or CH<sub>2</sub>R<sup>4</sup>,

R<sup>2</sup> = an optionally mono- or poly-Hal-substituted, linear or branched alkyl moiety having 1-6 C atoms, or an alkaryl, alk heteroaryl, or heteroaryl moiety,

R<sup>4</sup> = OH, OA, NH<sub>2</sub>, NHB or NB<sub>2</sub>,

A, B = independently of one another alkyl having 1-6 C atoms,

m = 2, 3, 4, 5 or 6 and

n = 0, 1, 2, 3 or 4,

or physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios.

See the specification at page 2, line 14 through page 3, line 2.

**(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

The rejection under 35 U.S.C. 112, second paragraph of claim 4.

The rejection of claims 1-4, 6-9 and 12-14 under 35 U.S.C. 102.

The rejection of claims 1, 3, 4, 6 and 14 under the doctrine of obviousness-type double patenting.

It is noted that, although the Advisory Action in item 7 indicates that the claims rejected are claims 1, 4, 6-9 and 11-14, claim 3 was subjected to the double patenting rejection at page 7 of the Final Rejection, and it is treated as having been so rejected herein.

It is also noted that the Advisory Action, at page 2, indicates that the amendments overcome “the” rejection under 35 U.S.C. 112, first paragraph. Two rejections under first paragraph were made in the Final Rejection, one applied to claims 1-4, 6-9 and 11-14, and a second rejection applied to claims 11-13. It is assumed that *both* of these rejections have been eliminated, based on this comment in the Advisory Action.

**(vii) ARGUMENT**

***Rejection Under 35 U.S.C. 112, Second Paragraph***

Claim 4 has been rejected under 35 U.S.C. § 112, second paragraph. It was argued in the Final Rejection that it is unclear what “alcohol protecting groups” are referred to in the claim. Indeed, protection of alcohol protecting groups is conventional and would be well understood by one of ordinary skill in the art with even a basic understanding of organic chemistry. The fact that the specification does not spell out specific alcohol protecting groups is in no way dispositive of indefiniteness. However, in order to expedite prosecution, the term was previously cancelled. Although the Advisory Action does not comment, it is submitted that the rejection should not be maintained.

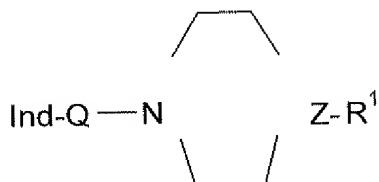
**Double Patenting**

Claims 1, 3, 4, 6 and 14 have been rejected under the Doctrine of obviousness-type double patenting. However, while the statement of the rejection in the Final Rejection references application serial no. 10/539,516, the detailed discussion of the rejection, on the other hand, references application serial no. 10/481,270. Accordingly, applicants were unable to determine which application is intended in the rejection. A request for clarification and for a new Office Action was mailed on August 27, 2008. That request has gone unanswered. The Advisory Action clarifies that it was the ‘270 application intended. Thus, for the first time, Appellants can respond to this issue. It is respectfully submitted that the claims of the ‘270 application in no way suggests the present claims, inasmuch as the compounds of the ‘270 application are unsubstituted at the nitrogen atom of the indole moiety. Inasmuch as the claims of the co-pending application do not suggest substitution at this important position, it

is submitted that they do not render obvious the present claims, and that the double-patenting rejection should be overturned. The same is respectfully requested.

Claims 1-4, 6-9 and 11-14 remain rejected under 35 U.S.C. § 102(b) over Bottcher '241, over Bathe '794 and over Bartoszyk '989. Although applicants provided a detailed discussion of these references in their prior reply, noting how the disclosures of the references *do not* disclose any compounds within the present scope, the Final Rejection maintained the rejection arguing that the “compounds have valid groups form [sic, from] compounds of instant claim 1.” On the one hand, this is not an adequate standard for anticipation. See *In re Marshall*, 577 F.2d 301, 198 U.S.P.Q. 344 (CCPA 1978), holding that all material elements of a claim must be disclosed in a reference for that reference to anticipate. While applicants do not fully understand this sentence at the bottom of page 8 of the Final Rejection, it is submitted that the disclosures of the references do not disclose compounds within the present scope, i.e., do not provide any anticipatory species, and that the present claims do not read on the reference.

In particular, Bottcher discloses compounds of the formula



wherein “Ind” is an “indol-3-yl radical which is unsubstituted or mono or polysubstituted” by various moieties. It is clear from this disclosure, e.g., at column 2, defining “Ind” as an indol-3-yl radical *substituted in the 5-position*, and moreover by the species of the examples, which disclose 5-substituted indoles, that the patent fails to suggest indoles which are substituted *on* the *nitrogen atom*, i.e., 1-substituted. Note that the presently claimed compounds are substituted in the 1 position (on a nitrogen atom) by R<sup>2</sup>, which is alkyl which may be mono or polysubstituted by halogen, or is alkaryl, alk heteroaryl, or heteroaryl. It is thus clear that the patent fails to anticipate such claims. Withdrawal of the rejection is therefore respectfully requested.

As with Bottcher, Bathe discloses only compounds which are unsubstituted on the

nitrogen atom of an indole moiety. Note that the compounds of Bathe are 5-cyano. Accordingly, the publication also fails to anticipate the present claims.

Finally, Bartoszyk also fails to disclose N-substituted indoles. Note that the '989 disclosure is directed to new indications for use of the compounds disclosed in Bottcher '241, at page 3, lines 6-10. Other compounds disclosed similarly lack the above-noted substitution. See page 2, lines 23-28, disclosing 5-cyano indols and 1H indols. Accordingly, this reference also fails to anticipate the present claims. It is submitted that, should these rejections be maintained, it is incumbent upon the office to provide an explanation of where, in each reference, an anticipatory disclosure is to be found, inasmuch as none of the references disclose N-substituted indoles. Withdrawal of the rejection is again respectfully requested.

Finally, the Final Rejection mentions WO 02/083666 as "prior art" but does not apply the disclosure in a rejection. Thus, no comment thereon is deemed necessary.

The above discussion clearly supports that there is ample basis to overturn the rejections of record, and the same is respectfully requested.

Respectfully submitted,

/Harry B. Shubin/

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Harry B. Shubin (Reg. No. 32,004)  
Attorney for Applicant(s)

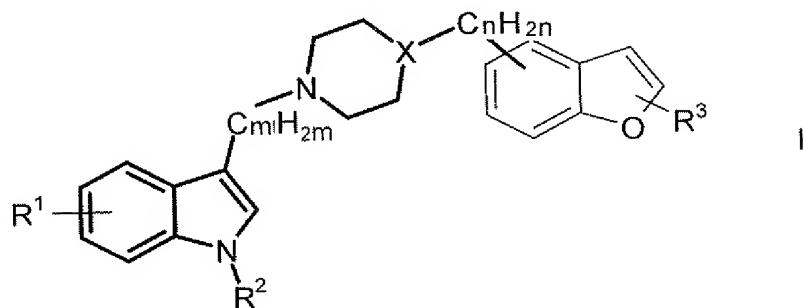
MILLEN, WHITE, ZELANO  
& BRANIGAN, P.C.  
Arlington Courthouse Plaza 1, Suite 1400  
2200 Clarendon Boulevard  
Arlington, Virginia 22201  
Telephone: (703) 243-6333  
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-3100

Date: March 6, 2009

**(viii) CLAIMS APPENDIX**

1. Compounds of the formula I



X = N or CH,

R<sup>1</sup>, R<sup>3</sup> = independently of one another H, OH, OA, CN, Hal, COR<sup>4</sup> or CH<sub>2</sub>R<sup>4</sup>,

R<sup>2</sup> = an optionally mono- or poly-Hal-substituted, linear or branched alkyl moiety having 1-6 C atoms, or an alkaryl, alkheteroaryl, or heteroaryl moiety,

R<sup>4</sup> = OH, OA, NH<sub>2</sub>, NHB or NB<sub>2</sub>,

A, B = independently of one another alkyl having 1-6 C atoms,

m = 2, 3, 4, 5 or 6 and

n = 0, 1, 2, 3 or 4,

or physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which

X = N,

R<sup>1</sup>, R<sup>3</sup> = independently of one another CN, COR<sup>4</sup> or CH<sub>2</sub>R<sup>4</sup>,

R<sup>2</sup> = a linear or branched alkyl having 1-6 C atoms, alkaryl, alkheteroaryl, or heteroaryl,

R<sup>4</sup> = OH, NH<sub>2</sub>, NHB or NB<sub>2</sub>,

A, B = independently of one another alkyl having 1-6 C atoms,

m = 4 and

n = 0,

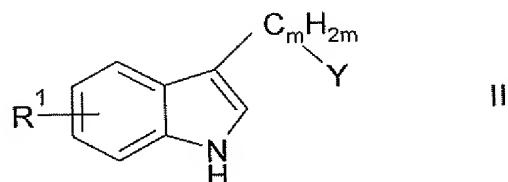
and physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2

- a. 5-{4-[4-(5-cyano-1-methyl-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide
- b. 5-{4-[4-(5-cyano-1-ethyl-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide
- c. 5-{4-[4-(5-cyano-1-isopropyl-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide
- d. 5-{4-[4-(1-benzyl-5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide
- e. 5-{4-[4-(5-cyano-1-propyl-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide
- f. 5-{4-[4-(5-cyano-1-pyridin-2-ylmethyl-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide
- g. 5-{4-[4-(5-cyano-1-phenethyl-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide

4. Process for the preparation of the compounds of the formula I, comprising

- a) reacting a compound of the formula II, in which R<sup>1</sup> and m have the meanings indicated in Claim 1 and Y is a halogen,



with a compound of the formula III, in which R<sup>2</sup> has the meanings indicated in

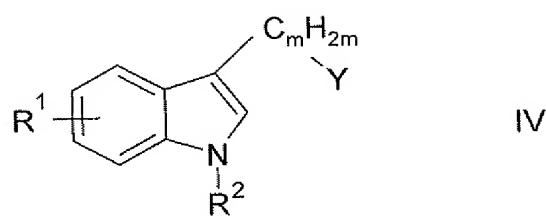
Claim 1 and Z represents a leaving group

$R^2 - Z$

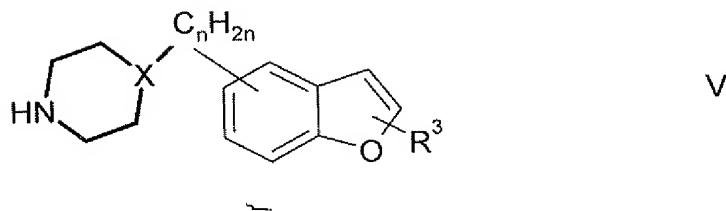
III

and

b) reacting a compound of the formula IV



obtained in accordance with a) with a compound of the formula V or a salt thereof, in which  $R^3$ , X and n have the meanings indicated in Claim 1,



in a solvent, optionally with addition of base, at the boiling point of the solvent,

or

c) converting a base of a compound of the formula I into one of its salts by treatment with an acid.

6. Pharmaceutical composition comprising at least one compound according to Claim 1 and/or physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios, and a pharmaceutically acceptable carrier.

7. Pharmaceutical composition, according to Claim 6 comprising further excipients and/or adjuvants.

8. Pharmaceutical composition comprising at least one compound according to Claim 1 and/or physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

9. Process for the preparation of a pharmaceutical composition, comprising bringing a compound according to Claim 1 and/or one of its physiologically acceptable salts or stereoisomers, including mixtures thereof in all ratios, into a suitable dosage form together with a solid, liquid or semi-liquid excipient or adjuvant.

12. A method of achieving an anxiolytic, antidepressant, neuroleptic and/or antihypertonic effect and/or for positively influencing obsessive-compulsive disorder (OCD), sleeping disorders, tardive dyskinesia, learning disorders, age-dependent memory disorders, eating disorders, and/or sexual dysfunctions, comprising administering to a host in need thereof an effective amount of a compound according to claim 1 and/or physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios.

14. A kit consisting of separate packs of

- a) an effective amount of a compound according to Claim 1 and/or physiologically acceptable salts or stereoisomers thereof, including mixtures thereof in all ratios, and
- b) an effective amount of a further medicament active ingredient.

**(ix) EVIDENCE APPENDIX**

None

**(x) RELATED PROCEEDINGS APPENDIX**

None